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|            |         |       |        |

DATE: Friday, February 09, 2007

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|-------|--------------------|--|---------------------|
|       | DB=PC              | GPB, USPT; PLUR=YES; OP=OR   | ,                   |
|       | L8                 | GPB, USPT; PLUR=YES; OP=OR  L6 and pet\$5.clm.  Of Interference  Search graph 2/9/07   | 1                   |
|       | L7                 | L6 and saxena.in.  | 2                   |
|       | L6                 | ((rnase\$4 or ribonucleas\$4) same pipien\$4) and (gene\$4 or cdna\$4 or dna\$4 or mrna\$4 or polynucleotid\$4 or nucleic\$4).clm.   | 29                  |
|       | DB=P               | GPB, USPT, EPAB, JPAB, DWPI; PLUR=YES; OP=OR   |                     |
|       | L5                 | 11 and saxena.in.  | 2                   |
|       | L4                 | L3 same (isolat\$\$ or clon\$4 or characteri\$4 or recombinan\$4 or purif\$4 or express\$4)  | 20                  |
|       | L3                 | L1 same (gene\$4 or cdna\$4 or dna\$4 or mrna\$4 or polynucleotid\$4 or nucleic\$4)  | 23                  |
|       | L2                 | L1 same tumo\$4  | 36                  |
|       | L1                 | (rnase\$4 or ribonucleas\$4) same pipien\$4  | 47                  |
| END O | F SEAR             | L1 same tumo\$4 (rnase\$4 or ribonucleas\$4) same pipien\$4  CH HISTORY  Regular  Jacob Market Ma |                     |

(FILE 'HOME' ENTERED AT 12:20:26 ON 09 FEB 2007)

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 12:20:43 ON 09 FEB 2007 SEA (RNAS? OR RIBONUCLEAS?)(S)PIPIEN?

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1 FILE ADISCTI
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- 5 FILE AQUASCI
- 2 FILE BIOENG
- 29 FILE BIOSIS
- **5 FILE BIOTECHABS**
- 5 FILE BIOTECHDS
- . 10 FILE BIOTECHNO
- 2 FILE CABA
- 36 FILE CAPLUS
- 1 FILE CIN
- 4 FILE DDFU
- 90 FILE DGENE
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- 17 FILE EMBASE
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- 20 FILE SCISEARCH
- 33 FILE TOXCENTER
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- 4 FILE USPAT2
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- **FILE WPINDEX**
- 6 FILE NLDB
- QUE (RNAS? OR RIBONUCLEAS?)(S) PIPIEN? L1

D RANK

FILE 'USPATFULL, CAPLUS, TOXCENTER, BIOSIS, SCISEARCH, MEDLINE, EMBASE, ESBIOBASE, LIFESCI, GENBANK' ENTERED AT 12:22:17 ON 09 FEB 2007

- L2 237 SEA (RNAS? OR RIBONUCLEAS?)(S) PIPIEN?
- 193 SEA L2 (S)(GENE? OR DNA? OR RNA? OR MRNA? OR CDNA? OR POLYNUCLE L3 OTI? OR NUCLEIC?)
- 126 SEA L3 (S)(ISOLÁT? OR CLON? OR CHARACTER? OR PURIF? OR L4 EXPRESS? OR RECOMBINAN?)
- L5 61 DUP REM L4 (65 DUPLICATES REMOVED)

  - D IBIB ABS L5 1 2 5 13 16 28 30 31 32 37 40 44 47 48 53

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TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS
                 "Ask CAS" for self-help around the clock
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        OCT 23
                 The Derwent World Patents Index suite of databases on STN
                 has been enhanced and reloaded
         OCT 30
                 CHEMLIST enhanced with new search and display field
NEWS
         NOV 03
                 JAPIO enhanced with IPC 8 features and functionality
NEWS
        NOV 10
                 CA/CAplus F-Term thesaurus enhanced
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         NOV 10
                 STN Express with Discover! free maintenance release Version
                 8.01c now available
NEWS
        NOV 20
                 CA/CAplus to MARPAT accession number crossover limit increased
                 to 50,000
         DEC 01
NEWS
                 CAS REGISTRY updated with new ambiguity codes
NEWS 10
        DEC 11
                 CAS REGISTRY chemical nomenclature enhanced
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        DEC 14
                 WPIDS/WPINDEX/WPIX manual codes updated
NEWS 12
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                 GBFULL and FRFULL enhanced with IPC 8 features and
                 functionality
        DEC 18
NEWS 13
                 CA/CAplus pre-1967 chemical substance index entries enhanced
                 with preparation role
NEWS 14
        DEC 18
                 CA/CAplus patent kind codes updated
NEWS 15
        DEC 18
                 MARPAT to CA/CAplus accession number crossover limit increased
                 to 50,000
NEWS 16 DEC 18
                 MEDLINE updated in preparation for 2007 reload
NEWS 17 DEC 27
                 CA/CAplus enhanced with more pre-1907 records
NEWS 18 JAN 08
                 CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 19 JAN 16
                 CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 20 JAN 16
                IPC version 2007.01 thesaurus available on STN
NEWS 21 JAN 16
                WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 22 JAN 22
                 CA/CAplus updated with revised CAS roles
NEWS 23 JAN 22
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NEWS 24 JAN 29
                 PHAR reloaded with new search and display fields
NEWS 25
       JAN 29
                 CAS Registry Number crossover limit increased to 300,000 in
                 multiple databases
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NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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=> index bioscience medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE TOTAL ENTRY SESSION 0.21 0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 12:20:43 ON 09 FEB 2007

#### 71 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view search error messages that display as 0\* with SET DETAIL OFF.

- => s (rnas? or ribonucleas?)(s)pipien?
  - 1 FILE ADISCTI
  - 5 FILE AQUASCI
  - 2 FILE BIOENG
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  - 5 FILE BIOTECHABS
  - 5 FILE BIOTECHDS
  - 10 FILE BIOTECHNO
  - 2 FILE CABA
  - 36 FILE CAPLUS
  - 1 FILE CIN
  - 4 FILE DDFU
  - 90 FILE DGENE
  - 2 FILE DISSABS
  - 25 FILES SEARCHED...
    - 6 FILE DRUGU
    - 17 FILE EMBASE
    - 16 FILE ESBIOBASE
    - 12 FILE GENBANK
    - 6 FILE IFIPAT
    - 6 FILE IMSDRUGNEWS
    - 1 FILE IMSRESEARCH
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  - 61 FILES SEARCHED...
    - 4 FILE USPAT2
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  - 35 FILES HAVE ONE OR MORE ANSWERS, 71 FILES SEARCHED IN STNINDEX
- L1 QUE (RNAS? OR RIBONUCLEAS?)(S) PIPIEN?

| => d rank |    |             |
|-----------|----|-------------|
| F1        | 90 | DGENE       |
| F2        | 39 | USPATFULL   |
| F3        | 36 | CAPLUS      |
| F4        | 33 | TOXCENTER   |
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| F6        | 20 | SCISEARCH   |
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| F17       | 6  | NLDB        |
| F18       | 5  | AQUASCI .   |
| F19       | 5  | BIOTECHABS  |
| F20       | 5  | BIOTECHDS   |
| F21       | 5  | PASCAL      |
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| F31       | 1  | ADISCTI     |
| F32       | 1  | CIN         |
| F33       | 1  | IMSRESEARCH |
| F34       | 1  | PHARMAML    |
| F35       | 1  | PROUSDDR    |

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SINCE FILE TOTAL ENTRY SESSION 1.89 2.10

FULL ESTIMATED COST

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L5 ANSWER 10 OF 61 USPATFULL on STN

TI Non-antigenic toxin-conjugate and fusion protein of internalizing receptor system

- L5 ANSWER 11 OF 61 USPATFULL on STN
- TI Methods of and compositions for inhibiting the proliferation of mammalian cells
- L5 ANSWER 12 OF 61 USPATFULL on STN
- TI Albumin fusion proteins
- L5 ANSWER 13 OF 61 USPATFULL on STN
- TI Recombinant anti-tumor RNAse
- L5 ANSWER 14 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN
- TI Recombinant production in mammalian cells of immunotoxins containing cytotoxic ribonuclease, such as ranpirnase, fused to an immunoglobulin, and therapeutic uses
- L5 ANSWER 15 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
- TI Efficient killing of CD22+ tumor cells by a humanized diabody-RNase fusion protein
- L5 ANSWER 16 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2
- TI Status of RNAs, localized in Xenopus laevis oocytes, in the frogs Rana pipiens and Eleutherodactylus coqui
- L5 ANSWER 17 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
- TI Recombinant autocyclized and cysteinized ranpirnase containing cleavable PelB leader peptide and Met23-L and Ser72-Cys mutations, its cDNA and expression vector, and methods of making them
- L5 ANSWER 18 OF 61 USPATFULL on STN
- TI Antibody/receptor targeting moiety for enhanced delivery of armed ligand
- L5 ANSWER 19 OF 61 USPATFULL on STN
- TI Antibody/receptor targeting moiety for enhanced delivery of armed ligand
- L5 ANSWER 20 OF 61 Elsevier BIOBASE COPYRIGHT 2007 Elsevier Science B.V. on STN DUPLICATE
- TI trans-Packaged west nile virus-like particles: Infectious properties in vitro and in infected mosquito vectors
- L5 ANSWER 21 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5
- TI Removal of N-terminal methionine from recombinant proteins by engineered E. coli methionine aminopeptidase
- L5 ANSWER 22 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 6
- TI Treatment of Jurkat acute T-lymphocytic leukemia cells by onconase (Ranpirnase) is accompanied by an altered nucleocytoplasmic distribution and reduced expression of transcription factor NF-κB
- ANSWER 23 OF 61 Elsevier BIOBASE COPYRIGHT 2007 Elsevier Science B.V.
- TI Quantitative analysis, using MALDI-TOF mass spectrometry, of the N-terminal hydrolysis and cyclization reactions of the activation process of onconase
- L5 ANSWER 24 OF 61 USPATFULL on STN
- TI Albumin fusion proteins
- L5 ANSWER 25 OF 61 USPATFULL on STN
- TI Methods for reduced renal uptake of protein conjugates
- L5 ANSWER 26 OF 61 USPATFULL on STN
- TI Immunoconjugates of toxins directed against malignant cells
- L5 ANSWER 27 OF 61 USPATFULL on STN

- TI Immunotoxins directed against malignant cells
- L5 ANSWER 28 OF 61 USPATFULL on STN
- TI Recombinant onconase and chemical conjugates and fusion proteins of recombinant onconase
- L5 ANSWER 29 OF 61 USPATFULL on STN
- TI Non-antigenic toxin-conjugate and fusion protein of internalizing receptor system
- L5 ANSWER 30 OF 61 USPATFULL on STN
- TI Recombinant anti-tumor RNAse
- L5 ANSWER 31 OF 61 USPATFULL on STN
- TI Mutant form of cytotoxic ribonucleolytic protein which allows production by recombinant methods
- L5 ANSWER 32 OF 61 USPATFULL on STN
- TI Mutant form of a cytotoxic ribonucleolytic protein which allows production by recombinant methods
- L5 ANSWER 33 OF 61 Elsevier BIOBASE COPYRIGHT 2007 Elsevier Science B.V. on STN DUPLICATE
- TI The structural integrity exerted by N-terminal pyroglutamate is crucial for the cytotoxicity of frog ribonuclease from Rana pipiens
- L5 ANSWER 34 OF 61 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
- TI Treatment of human Daudi lymphoma with anti-MUC1 antibody-targeted RNase in SCID mice.
- L5 ANSWER 35 OF 61 USPATFULL on STN
- TI Immunotoxins, comprising an internalizing antibody, directed against malignant and normal cells
- L5 ANSWER 36 OF 61 USPATFULL on STN
- TI METHODS FOR REDUCED RENAL UPTAKE OF PROTEIN CONJUGATES
- L5 ANSWER 37 OF 61 USPATFULL on STN
- TI Methods of making nucleic acids encoding ribonucleases
- L5 ANSWER 38 OF 61 USPATFULL on STN
- TI Method of treatment with a non-antigenic toxin-conjugate and fusion protein of internalizing receptor system
- L5 ANSWER 39 OF 61 USPATFULL on STN
- TI Immunotoxins directed against malignant cells
- L5 ANSWER 40 OF 61 USPATFULL on STN
- TI Nucleic acids encoding ribonucleases and methods of making them
- L5 ANSWER 41 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 8
- TI Mechanism of ribonuclease cytotoxicity
- L5 ANSWER 42 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 9
- TI Rapid Diversification of RNase A Superfamily Ribonucleases from the Bullfrog, Rana catesbeiana
- L5 ANSWER 43 OF 61 TOXCENTER COPYRIGHT 2007 ACS on STN
- TI Mechanism of ribonuclease cytotoxicity
- L5 ANSWER 44 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 10
- TI Purification and sequences of RNase-like glycoproteins from Rana pipiens and their use in the treatment of tumors

- L5 ANSWER 45 OF 61 USPATFULL on STN
- TI Non-antigenic toxin-conjugate and fusion protein of internalizing receptor system
- L5 ANSWER 46 OF 61 USPATFULL on STN
- TI Recombinant ribonuclease proteins
- L5 ANSWER 47 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 11
- TI A gender-specific mRNA encoding a cytotoxic ribonuclease contains a 3' UTR of unusual length and structure
- L5 ANSWER 48 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 12
- TI Recombinant anti-tumor RNase
- L5 ANSWER 49 OF 61 USPATFULL on STN
- TI Selective RNase cytotoxic reagents
- L5 ANSWER 50 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 13
- TI Onconase immunotoxins directed against malignant B-cells
- L5 ANSWER 51 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 14
- TI The solution structure of a cytotoxic ribonuclease from the oocytes of Rana catesbeiana (bullfrog)
- L5 ANSWER 52 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 15
- TI Amino acid-substituted analogs of the cytostatic, cytotoxic ribonuclease Onconase that can be manufactured on a large scale
- L5 ANSWER 53 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN
- TI Recombinant ribonuclease proteins and their use for killing tumor cells
- L5 ANSWER 54 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN
- TI Expression and characterization of a cytotoxic human-frog chimeric ribonuclease: potential for cancer therapy
- L5 ANSWER 55 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 16
- TI Anti-tumor ribonuclease, combined with or conjugated to monoclonal antibody MRK16, overcomes multidrug resistance to vincristine in vitro and in vivo
- L5 ANSWER 56 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 17
- TI Enhancement of vincristine cytotoxicity in drug-resistant cells by simultaneous treatment with onconase, an antitumor ribonuclease
- L5 ANSWER 57 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 18
- TI Toxicity of an antitumor ribonuclease to Purkinje neurons
- L5 ANSWER 58 OF 61 LIFESCI COPYRIGHT 2007 CSA on STN
- TI A cytotoxic ribonuclease: Study of the mechanism of onconase cytotoxicity.
- L5 ANSWER 59 OF 61 LIFESCI COPYRIGHT 2007 CSA on STN
- TI Cytotoxic onconase and ribonuclease A chimeras: Comparison and in vitro characterization.
- L5 ANSWER 60 OF 61 LIFESCI COPYRIGHT 2007 CSA on STN
- TI Sequence and expression of a frog brain complementary DNA encoding a kainate-binding protein.
- L5 ANSWER 61 OF 61 GENBANK® COPYRIGHT 2007 on STN
  - TITLE (TI): Recombinant anti-tumor rnase
- => d ibib abs 15 1 2 5 13 16 28 30 31 32 37 40 44 47 48 53

ANSWER 1 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2007:4344 USPATFULL

TITLE: Cytotoxic ribonuclease variants

Raines, Ronald T., Madison, WI, UNITED STATES INVENTOR(S): Mitchell, Julie C., Madison, WI, UNITED STATES

Rutkoski, Thomas J., Madison, WI, UNITED STATES

KIND DATE NUMBER \_\_\_\_\_\_ US 2007003537 A1 20070104

US 2006-454379 APPLICATION INFO.: A1 20060616 (11)

> NUMBER DATE

US 2005-690970P 20050616 (60) PRIORITY INFORMATION:

DOCUMENT TYPE: Utility APPLICATION FILE SEGMENT:

QUARLES & BRADY LLP, FIRSTAR PLAZA, ONE SOUTH PINCKNEY LEGAL REPRESENTATIVE:

STREET, P.O. BOX 2113 SUITE 600, MADISON, WI,

53701-2113, US

NUMBER OF CLAIMS: 11 EXEMPLARY CLAIM: 1

PATENT INFORMATION:

3 Drawing Page(s) NUMBER OF DRAWINGS:

LINE COUNT: 818

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

This invention relates to altered forms of members of the RNase A superfamily. An RNase A can be modified to be cytotoxic by altering its amino acid sequence so that it is not bound easily by the ribonuclease inhibitor while still retaining catalytic properties. While earlier work had identified some modifications to RNase A that would result in cytotoxicity, the use of the FADE algorithm for molecular interaction analysis has led to several other locations that were candidates for modification. Some of those modifications did result in RNase A variants with increase cytotoxicity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ANSWER 2 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2006:340357 USPATFULL

Cytotoxic ribonuclease variants TITLE:

Raines, Ronald T., Madison, WI, UNITED STATES INVENTOR(S):

Phillips, George N. JR., Madison, WI, UNITED STATES Johnson, R. Jeremy, Middleton, WI, UNITED STATES

McCoy, Jason G., Madison, WI, UNITED STATES

NUMBER KIND DATE \_\_\_\_\_ US 2006292137 A1 20061228 US 2006-454418 A1 20060616 (11) PATENT INFORMATION:

APPLICATION INFO.:

NUMBER DATE -----

PRIORITY INFORMATION: US 2005-691311P 20050616 (60)

DOCUMENT TYPE: Utility APPLICATION FILE SEGMENT:

QUARLES & BRADY LLP, FIRSTAR PLAZA, ONE SOUTH PINCKNEY LEGAL REPRESENTATIVE:

STREET, P.O. BOX 2113 SUITE 600, MADISON, WI,

53701-2113, US

NUMBER OF CLAIMS: 23 EXEMPLARY CLAIM:

1

NUMBER OF DRAWINGS: 5 Drawing Page(s)

LINE COUNT: 1560

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

This invention relates to cytotoxic variants of human ribonuclease 1 (RNase 1) identified through analysis of the interaction between RNase 1 and the human ribonuclease inhibitor (hRI) as defined by the three dimensional (3-D) atomic structure of the RNase 1 hRI complex. Also disclosed is the 3-D structure of the hRI.RNase 1 complex and methods for designing the RNase 1 variants.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2006:15863 USPATFULL

TITLE: Fusion proteins containing recombinant cytotoxic RNAses

INVENTOR(S): Goldenberg, David M., Mendham, NJ, UNITED STATES

Hansen, Hans J., Picayune, MS, UNITED STATES
Chang, Chien-Hsing, Downingtown, PA, UNITED STATES
Vanama, Sailaja, Morristown, NJ, UNITED STATES

Rossi, Edmund A., Nutley, NJ, UNITED STATES

PATENT ASSIGNEE(S): Immunomedics, Inc., Morris Plains, NJ, UNITED STATES

(U.S. corporation)

NUMBER DATE

PRIORITY INFORMATION: US 2004-544227P 20040213 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Heller Ehrman White & McAuliffe, Suite 300, 1666 K

\_\_\_\_\_

Street, N.W., Washington, DC, 20006, US

NUMBER OF CLAIMS: 40 EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 14 Drawing Page(s)

LINE COUNT: 1524

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Recombinant immunotoxins containing a cytotoxic RNAse fused to an antibody or antibody fragment may be produced in mammalian cell culture. Surprisingly, immunotoxins containing a cytotoxic RNAse fused to the N-terminus of one antibody variable domain can be prepared and retain the ability to specifically bind antigen. The immunotoxins may be used in a variety of therapeutic methods for treating diseases or syndromes associated with unwanted or inappropriate cell proliferation or activation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 13 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2005:71048 USPATFULL

TITLE: Recombinant anti-tumor RNAse

INVENTOR(S): Rybak, Susanna M., Frederick, MD, United States

Newton, Dianne L., Rockville, MD, United States The United States of America as represented by the

PATENT ASSIGNEE(S): The United States of America as represented by the

Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S.

government)

|                     | NUMBER         | KIND | DATE     |              |
|---------------------|----------------|------|----------|--------------|
| PATENT INFORMATION: | US 6869604     | B1   | 20050322 |              |
|                     | WO 9950398     |      | 19991007 |              |
| APPLICATION INFO.:  | US 2001-622613 |      | 20010731 | (9)          |
|                     | WO 1999-US6641 |      | 19990326 |              |
|                     |                |      | 20010731 | PCT 371 date |

NUMBER DATE

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PRIORITY INFORMATION: US 1998-79751P 19980327 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Helms, Larry R. ASSISTANT EXAMINER: Yu, Misook

LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP

NUMBER OF CLAIMS: 23 EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)

LINE COUNT: 2572

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

This invention provides for new recombinant ribonuclease proteins which are active when expressed by bacteria. This allows the recombinant ribonucleases of this invention to be fused in-frame with ligand binding moieties to form cytotoxic fusion proteins. Furthermore, these proteins are more active than ribonucleases currently available even though the proteins of this invention lack an N-terminal pyroglutamic acid, which has been found to be necessary for ribonucleolytic activity. Because these proteins are recombinant proteins, mutations which increase cytotoxicity can be engineered.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 16 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:217226 CAPLUS

DOCUMENT NUMBER: 142:407935

AUTHOR (S):

TITLE: Status of RNAs, localized in Xenopus laevis oocytes,

in the frogs Rana pipiens and Eleutherodactylus coqui Nath, Kimberly; Boorech, Jamie L.; Beckham, Yvonne M.;

Burns, Mary M.; Elinson, Richard P.

CORPORATE SOURCE: Department of Biological Sciences, Duquesne

University, Pittsburgh, PA, 15282, USA

SOURCE: Journal of Experimental Zoology, Part B: Molecular and

Developmental Evolution (2005), 304B(1), 28-39

CODEN: JEZPBS

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal LANGUAGE: English

AB Early development in the frog model, X. laevis, is governed by RNAs, localized to the vegetal cortex of the oocyte. These RNAs include Xdazl RNA, which is involved in primordial germ cell formation, and VegT RNA,

which specifies the mesoderm and endoderm. To determine whether orthologues of

these RNAs are localized and have similar functions in other

frogs, we cloned RpDazl and RpVegT from R. pipiens, a frog that is phylogenetically distant from X. laevis. RNAs from both genes are localized to the vegetal cortex of the R. pipiens oocyte, indicating that the vegetal localization is likely the basal state. The animal location of EcVegT RNA in E. coqui that we found previously is then a derived state, probably due to the great increase in egg size required for direct development of this species. To answer the question of function, we injected RpVegT or EcVegT RNAs into X. laevis embryos, and assayed animal caps for gene expression. Both of these RNAs induced the expression of endodermal, mesodermal, and organizer genes, showing that the function of RpVegT and EcVegT as mesoendodermal determinants is conserved in frogs. The RNA localizations and the function of VegT orthologues in germ layer specification may be synapomorphies for anuran amphibians.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2003:145885 USPATFULL

TITLE: Recombinant onconase and chemical conjugates and fusion

proteins of recombinant onconase

INVENTOR(S): Goldenberg, David M., Mendham, NJ, UNITED STATES

Hansen, Hans, Picayune, MS, UNITED STATES

Leung, Shui-On, Morris Township, NJ, UNITED STATES

PATENT ASSIGNEE(S): Immunomedics, Inc. (U.S. corporation)

> NUMBER KIND

US 2003099629 A1 20030529 US 2002-153882 A1 20020524 (10) PATENT INFORMATION: APPLICATION INFO.:

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-265901, filed on 11

Mar 1999, ABANDONED

DOCUMENT TYPE: Utility FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW,

WASHINGTON, DC, 20007

NUMBER OF CLAIMS: EXEMPLARY CLAIM:

NUMBER OF DRAWINGS: 1 Drawing Page(s)

LINE COUNT: 941

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Recombinantly-produced Onconase molecules and fusion proteins containing the same are disclosed. The recombinantly-produced Onconase molecule has the sequence of native Onconase, retains the proper folding of native Onconase and has cytotoxic activity similar to that of Onconase purified from oocytes of Rana pipiens. cDNA coding for Onconase is extended by one triplet which codes for N-formyl-methionine. When expressed recombinantly, the mutant Onconase has N-formyl-methionine as the N-terminal amino acid, and glutaminyl as the penultimate N-terminal residue. Following expression, the N-formyl methionine residue is cleaved and the penultimate glutaminyl residues is cyclized to produce Onconase with an N-terminal pyroglutamate residue, and hence the same structure and function as native Onconase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ANSWER 30 OF 61 USPATFULL on STN

2003:37666 USPATFULL ACCESSION NUMBER:

Recombinant anti-tumor RNAse TITLE:

Rybak, Susanna M., Frederick, MD, UNITED STATES INVENTOR(S):

Newton, Dianne L., Rockville, MD, UNITED STATES

PATENT ASSIGNEE(S): The Department of Health and Human Services National

Institutes of Health, Rockville, MD, 20852 (U.S.

corporation)

NUMBER KIND DATE -----US 2003027311 A1 20030206 US 2001-948391 A1 20010906 (9) PATENT INFORMATION: APPLICATION INFO.:

Division of Ser. No. US 2001-622613, filed on 31 Jul RELATED APPLN. INFO.:

2001, PENDING A 371 of International Ser. No. WO

1999-US6641, filed on 26 Mar 1999, UNKNOWN

NUMBER DATE -----

PRIORITY INFORMATION: US 1998-79751P 19980327 (60)

DOCUMENT TYPE: Utility FILE SEGMENT: APPLICATION

TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO LEGAL REPRESENTATIVE:

CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834

NUMBER OF CLAIMS: EXEMPLARY CLAIM: LINE COUNT: 2625

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

This invention provides for new recombinant ribonuclease proteins which are active when expressed by bacteria. This allows the recombinant

ribonucleases of this invention to be fused in-frame with ligand binding moieties to form cytotoxic fusion proteins. Furthermore, these proteins are more active than ribonucleases currently available even though the proteins of this invention lack an N-terminal pyroglutamic acid, which has been found to be necessary for ribonucleolytic activity. Because these proteins are recombinant proteins, mutations which increase cytotoxicity can be engineered.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 31 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2003:302792 USPATFULL

TITLE: Mutant form of cytotoxic ribonucleolytic protein which

allows production by recombinant methods

INVENTOR(S): Youle, Richard J., Bethesda, MD, United States

Vasandani, Veena M., Rockville, MD, United States

Wu, Yon-Neng, Bethesda, MD, United States

Boix, Ester, Barcelona, SPAIN

Ardelt, Wojciech, New City, NY, United States

PATENT ASSIGNEE(S): The United States of America as represented by the

Department of Health and Human Services, Washington,

DC, United States (U.S. government)

NUMBER KIND DATE

PATENT INFORMATION: US 6649393 B1 20031118
APPLICATION INFO.: US 1998-95429 19980610 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-626288, filed on 4 Apr

1996

DOCUMENT TYPE: Utility FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Nashed, Nashaat T.

LEGAL REPRESENTATIVE: Klarquist Sparkman, LLP

NUMBER OF CLAIMS: 8 EXEMPLARY CLAIM: 1

INVENTOR(S):

NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)

LINE COUNT: 1477

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

The present invention provides recombinant Onc (rOnc) compositions and methods. Recombinant Onc proteins of the invention have an amino terminal methionine and comprise an Onc polypeptide. The amino terminal methionine of the protein allows for recombinant production in a bacterial host cell. Cleaving the amino terminal methionine exposes the amino terminal glutamine of the polypeptide. The Onc polypeptide has an amino terminal glutamine. Cyclization of the amino terminal glutamine of the polypeptide to a pyroglutamyl residue provides ronc polypeptides and proteins have anti-cancer and anti-viral activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 32 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2003:302791 USPATFULL

TITLE: Mutant form of a cytotoxic ribonucleolytic protein

which allows production by recombinant methods Youle, Richard J., Bethesda, MD, United States Vasandani, Veena M., Rockville, MD, United States

vasandani, veena M., kockviile, MD, oniced

Wu, Yon-Neng, Bethesda, MD, United States

Boix, Ester, Barcelona, SPAIN

Ardelt, Wojciech, New City, NY, United States

PATENT ASSIGNEE(S): The United States of America as represented by the

Department of Health and Human Services, Washington,

DC, United States (U.S. government)

NUMBER KIND DATE

PATENT INFORMATION: US 6649392 B1 20031118

APPLICATION INFO.: US 1996-626288 19960404 (8)

DOCUMENT TYPE: Utility FILE SEGMENT: GRANTED

FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Nashed, Nashaat T.
LEGAL REPRESENTATIVE: Klarquist Sparkman, LLP

NUMBER OF CLAIMS: 11 EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)

LINE COUNT: 1497

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

The present invention provides recombinant Onc (rOnc) compositions and methods. Recombinant Onc proteins of the invention have an amino terminal methionine and comprise an Onc polypeptide. The amino terminal methionine of the protein allows for recombinant production in a bacterial host cell. Cleaving the amino terminal methionine exposes the amino terminal glutamine of the polypeptide. The Onc polypeptide has an amino terminal glutamine. Cyclization of the amino terminal glutamine of the polypeptide to a pyroglutamyl residue provides ronc polypeptides and proteins have anti-cancer and anti-viral activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 37 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2002:181539 USPATFULL

TITLE: Methods of making nucleic acids encoding ribonucleases INVENTOR(S): Saxena, Shailendra K., West Orange, NJ, United States

PATENT ASSIGNEE(S): Alfacell Corporation, Bloomfield, NJ, United States

(U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION: US 6423515 B1 20020723
APPLICATION INFO.: US 2000-687748 20001014 (9)

APPLICATION INFO.. District of Garage May 100 204000 files

RELATED APPLN. INFO.: Division of Ser. No. US 1999-394268, filed on 10 Sep

1999, now patented, Pat. No. US 6175003

DOCUMENT TYPE: Utility FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Fredman, Jeffrey ASSISTANT EXAMINER: Einsmann, Juliet

NUMBER OF CLAIMS: 7 EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)

LINE COUNT: 329

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

pET11d-rOnc(Q1, M23L) DNA is subjected to two different site-directed mutations, each using an overlapping PCR protocol. One of the site-directed mutations changes the amino acid residue at position 23 of the encoded protein from leucine to methionine, whereby the encoded protein can be made into ranpirnase by cleaving the N-terminal methionine residue and allowing the adjacent glutamine residue to autocyclize. The other site-directed mutation changes the amino acid residue at position 72 of the encoded protein from serine to cysteine, thereby producing an encoded protein that can be made into a cysteinized ranpirnase by cleaving the N-terminal methionine residue and allowing the adjacent glutamine residue to autocyclize.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 40 OF 61 USPATFULL on STN

ACCESSION NUMBER: 2001:8169 USPATFULL

TITLE: Nucleic acids encoding ribonucleases and methods of

making them

INVENTOR(S): Saxena, Shailendra K., West Orange, NJ, United States PATENT ASSIGNEE(S): Alfacell Corporation, Bloomfield, NJ, United States

### (U.S. corporation)

NUMBER KIND DATE -----US 6175003 B1 20010116 PATENT INFORMATION: US 1999-394268 19990910 (9) APPLICATION INFO.: DOCUMENT TYPE: Utility Granted FILE SEGMENT: PRIMARY EXAMINER: Fredman, Jeffrey Einsmann, Juliet C. ASSISTANT EXAMINER: NUMBER OF CLAIMS: EXEMPLARY CLAIM: NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s) LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

pET11d-rOnc(Q1, M23L) DNA is subjected to two different site-directed mutations, each using an overlapping PCR protocol. One of the site-directed mutations changes the amino acid residue at position 23 of the encoded protein from leucine to methionine, whereby the encoded protein can be made into ranpirnase by cleaving the N-terminal methionine residue and allowing the adjacent glutamine residue to autocyclize. The other site-directed mutation changes the amino acid residue at position 72 of the encoded protein from serine to cysteine, thereby producing an encoded protein that can be made into a cysteinized ranpirnase by cleaving the N-terminal methionine residue and allowing the adjacent glutamine residue to autocyclize.

#### CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 44 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 10

ACCESSION NUMBER:

2000:475689 CAPLUS

DOCUMENT NUMBER:

133:101138

TITLE:

Purification and sequences of RNase

-like glycoproteins from Rana pipiens and

their use in the treatment of tumors

INVENTOR(S):

Ardelt, Wojciech

PATENT ASSIGNEE(S):

Alfacell Corporation, USA PCT Int. Appl., 32 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

SOURCE:

English

1

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE         | APPLICATION NO. |   | DATE     |  |  |  |
|------------------------|--------|--------------|-----------------|---|----------|--|--|--|
|                        |        |              |                 |   |          |  |  |  |
| WO 2000040608          | A1     | 20000713     | WO 1999-US30799 |   | 19991224 |  |  |  |
| W: JP                  |        |              |                 |   |          |  |  |  |
| RW: AT, BE, CH,        | DE, FR | , GB, IT, LU | , NL            |   |          |  |  |  |
| US 6239257             | B1     | 20010529     | US 1998-223118  |   | 19981230 |  |  |  |
| EP 1141004             | A1     | 20011010     | EP 1999-968949  |   | 19991224 |  |  |  |
| R: AT, BE, CH,         | DE, FR | , GB, IT, LI | , LU, NL        |   |          |  |  |  |
| JP 2002534075          | T      | 20021015     | JP 2000-592316  |   | 19991224 |  |  |  |
| PRIORITY APPLN. INFO.: |        |              | US 1998-223118  | Α | 19981230 |  |  |  |
|                        |        |              | WO 1999-US30799 | W | 19991224 |  |  |  |

AB Purification and physicochem. properties of four glycoproteins: 2325p4, 2325p4a, 2325p6 and 2728, that are bioactive against human tumor cell lines are disclosed. These glycoproteins are derived from eggs of the Rana pipiens frog, and are members of the superfamily of pancreatic RNases. Each RNase-like glycoprotein from Rana pipiens has (a) an amino acid sequence that is 114 amino acids long, (b) an isoelec. point of .apprx.10, and (c) a mol. weight of .apprx.13,000.

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 47 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2000:472150 CAPLUS

DOCUMENT NUMBER: 133:318111

TITLE: A gender-specific mRNA encoding a cytotoxic

ribonuclease contains a 3' UTR of unusual length and

structure

AUTHOR(S): Chen, Shin-Lin; Le, Shu-Yun; Newton, Dianne L.;

Maizel, Jacob V., Jr.; Rybak, Susanna M.

CORPORATE SOURCE: Laboratory of Biochemical Physiology and Division of

Basic Science, SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Development

Center, Frederick, MD, 21702, USA

SOURCE: Nucleic Acids Research (2000), 28(12), 2375-2382

CODEN: NARHAD; ISSN: 0305-1048

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal LANGUAGE: English

A cDNA (2855 nt) encoding a putative cytotoxic RNase (rapLR1) related to the antitumor protein onconase was cloned from a library derived from the liver of gravid female amphibian Rana pipiens. The cDNA was mainly comprised (83%) of 3' untranslated region (UTR). Secondary structure anal. predicted two unusual folding regions (UFRs) in the RNA 3' UTR. Two of these regions (711-1442 and 1877-2130 nt) contained remarkable, stalk-like, stem-loop structures greater than 38 and 12 standard deviations more stable than by chance, resp. Secondary structure modeling demonstrated similar structures in the 3' UTRs of other species at low frequencies (0.01-0.3%). The size of the rapLR1 cDNA corresponded to the major hybridizing RNA cross-reactive with a genomic clone encoding onconase (3.6 kb). The transcript was found only in liver mRNA from female frogs. In contrast, immunoreactive onconase protein was detected only in oocytes. Deletion of the 3' UTR facilitated the in vitro translation of the rapLR1 cDNA. Taken together these results suggest that these unusual UFRs may affect mRNA metabolism and/or translation.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 48 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 1999:640970 CAPLUS

DOCUMENT NUMBER: 131:283317

TITLE: Recombinant anti-tumor RNase

INVENTOR(S): Rybak, Susanna M.; Newton, Dianne L.

PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PA | PATENT NO. |     |     |     | KIND DATE   |     |                | 1    | APPL | ICAT: |      | DATE     |     |     |     |       |     |  |
|----|------------|-----|-----|-----|-------------|-----|----------------|------|------|-------|------|----------|-----|-----|-----|-------|-----|--|
|    |            |     |     |     | -           |     |                |      |      |       |      |          |     |     |     |       |     |  |
| WO | WO 9950398 |     |     | A2  | A2 19991007 |     |                | 1    | WO 1 | 999-1 |      | 19990326 |     |     |     |       |     |  |
| WO | 9950       | 398 |     |     | <b>A</b> 3  |     | 1999           | 1223 |      |       |      |          |     |     |     |       |     |  |
|    | W:         | ΑE, | AL, | AM, | ΑT,         | AU, | ΑZ,            | BA,  | BB,  | ВG,   | BR,  | BY,      | CA, | CH, | CN, | CU,   | CZ, |  |
|    |            | DE, | DK, | EE, | ES,         | FI, | GB,            | GD,  | GE,  | GH,   | GM,  | HR,      | HU, | ID, | IL, | IN,   | IS, |  |
|    |            | JP, | KΕ, | KG, | ΚP,         | KR, | KZ,            | LC,  | LK,  | LR,   | LS,  | LT,      | LU, | LV, | MD, | MG,   | MK, |  |
|    |            | MN, | MW, | MX, | NO,         | NZ, | $\mathtt{PL},$ | PT,  | RO,  | RU,   | SD,  | SE,      | SG, | SI, | SK, | SL,   | ТJ, |  |
|    |            | TM, | TR, | TT, | UA,         | UG, | US,            | UΖ,  | VN,  | YU,   | ZA,  | ZW,      | AM, | AZ, | BY, | KG,   | ΚZ, |  |
|    |            | MD, | RU, | ТJ, | TM          |     |                |      |      |       |      |          |     |     |     |       |     |  |
|    | RW:        | GH, | GM, | KE, | LS,         | MW, | SD,            | SL,  | SZ,  | UG,   | ZW,  | ΑT,      | BE, | CH, | CY, | DE,   | DK, |  |
|    |            | ES, | FI, | FR, | GB,         | GR, | ΙE,            | IT,  | LU,  | MC,   | NL,  | PT,      | SE, | BF, | ВJ, | CF,   | CG, |  |
|    |            | CI, | CM, | GΑ, | GN,         | GW, | ML,            | MR,  | NE,  | SN,   | TD,  | TG       |     |     |     |       |     |  |
| CA | 2324       | 646 |     |     | A1          |     | 1999           | 1007 | (    | CA 1  | 999- | 2324     | 646 |     | 19  | 9990: | 326 |  |
| CA | 2401       |     |     |     | A1          |     |                |      |      |       |      |          |     |     | 19  | 9990: | 326 |  |
| ΑU | 9932       | 074 |     |     | A           |     | 1999           | 1018 | 7    | AU 1  | 999- | 3207     | 4   |     | 19  | 9990: | 326 |  |

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AU 755147
                         B2
                                20021205
                                           EP 1999-914174
     EP 1068332
                         A2
                                20010117
        R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
                          A1
                                20030122
                                           EP 2002-78725
        R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI, CY
                                20050322
                                            US 2001-622613
     US 6869604
                                                                   20010731
     US 2003027311
                         A1
                                20030206
                                            US 2001-948391
                                                                   20010906
                                            US 2001-961400
     US 2003124131
                         A1
                                20030703
                                                                   20010925
                                            AU 2002-18855
     AU 773347
                         B2
                                20040520
                                                                   20020301
     AU 2002018855
                         A5
                                20020502
                                            US 1998-79751P
PRIORITY APPLN. INFO.:
                                                               P 19980327
                                            CA 1999-2324646
                                                               A3 19990326
                                            EP 1999-914174
                                                               A3 19990326
                                            WO 1999-US6641
                                                                W 19990326
                                            US 2001-622613
                                                                A3 20010731
     This invention provides for new recombinant RNase proteins which are
AB
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active when expressed by bacteria. This allows the recombinant RNases of this invention to be fused in-frame with ligand binding moieties to form cytotoxic fusion proteins. Furthermore, these proteins are more active than RNases currently available even though the proteins of this invention lack an N-terminal pyroglutamic acid, which has been found to be necessary for ribonucleolytic activity. Because these proteins are recombinant proteins, mutations which increase cytotoxicity can be engineered. Thus, the cDNA for the RNase of Rana pipiens liver was cloned and sequenced. The enzyme was not recognized by antibodies to Onconase. The cDNA for the liver RNase encoded a signal sequence-containing protein which displayed 4 amino acid changes relative to Onconase. The Q1S mutant of this enzyme was produced with recombinant Escherichia coli. This mutant had higher RNase activity than did the corresponding Q1S mutant of Onconase. The R. catesbeiana RNase was also prepared with E. coli. This enzyme, which contained a normal pyroglutamate N-terminus, was .appix.20-fold more active than RNase. R. pipiens liver RNase, Q1S R. pipiens liver RNase, and R. catesbeiana RNase were all more cytotoxic to tumor cells than was Onconase.

ANSWER 53 OF 61 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:579829 CAPLUS

DOCUMENT NUMBER:

127:257613

TITLE:

Recombinant ribonuclease proteins and their use for

killing tumor cells

INVENTOR (S):

Rybak, Susanna M.; Newton, Dianne L.; Boque, Lluis;

Wlodawer, Alexander

PATENT ASSIGNEE(S):

Rybak, Susanna M., USA; Newton, Dianne L.; Boque, Lluis; Wlodawer, Alexander; United States Dept. of

Health and Human Services

SOURCE:

PCT Int. Appl., 90 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

| PATENT  | NO. KIND DATE |     |     |     |             |      |             | APPLICATION NO. |                 |     |     |     | DATE |          |     |     |    |
|---------|---------------|-----|-----|-----|-------------|------|-------------|-----------------|-----------------|-----|-----|-----|------|----------|-----|-----|----|
|         |               |     |     |     | -           |      | - <b></b> - |                 |                 |     |     |     |      | -        |     |     |    |
| WO 9731 | 1116 A        |     |     | A2  | A2 19970828 |      |             |                 | WO 1997-US2588  |     |     |     |      | 19970219 |     |     |    |
| W:      | AL,           | AM, | ΑT, | ΑU, | ΑZ,         | BA,  | BB,         | BG,             | BR,             | BY, | CA, | CH, | CN,  | CU,      | CZ, | DE, |    |
|         | DK,           | EE, | ES, | FI, | GB,         | GE,  | HU,         | IL,             | IS,             | JP, | KΕ, | KG, | KP,  | KR,      | ΚZ, | LC, |    |
|         | LK,           | LR, | LS, | LT, | LU,         | LV,  | MD,         | MG,             | MK,             | MN, | MW, | MX, | NO,  | NZ,      | ΡL, | PT, |    |
|         | RO,           | RU, | SD, | SE, | SG,         | SI,  | SK,         | TJ,             | TM,             | TR, | TT, | UA, | UG,  | US,      | UZ, | VN, | YU |
| RW:     | KE,           | LS, | MW, | SD, | SZ,         | UG,  | ΑT,         | BE,             | CH,             | DE, | DK, | ES, | FI,  | FR,      | GB, | GR, |    |
|         | ΙE,           | IT, | LU, | MC, | NL,         | PT,  | SE,         | BF,             | ВJ,             | CF, | CG, | CI, | CM,  | GA,      | GN, | ML, |    |
|         | MR,           | ΝE, | SN, | TD, | TG          |      |             |                 |                 |     |     |     |      |          |     |     |    |
| CA 2245 | 804           |     |     | A1  |             | 1997 | 0828        |                 | CA 1997-2245804 |     |     |     |      | 19970219 |     |     |    |

| CA      | 22458 | B04   |     |     | C       | 200    | 70123 |        |        |       |     |     |       |            |     |
|---------|-------|-------|-----|-----|---------|--------|-------|--------|--------|-------|-----|-----|-------|------------|-----|
| AU      | 97213 | 306   |     |     | Α       | 199    | 70910 | AU     | 1997-  | 21306 | ;   |     | 199   | 702        | 19  |
| AU      | 7263  | 79    |     |     | B2      | 200    | 01102 |        |        |       |     |     |       |            |     |
| EP      | 89662 | 25    |     |     | A2      | 199    | 90217 | EP     | 1997-  | 90667 | 5   |     | 199   | 9702       | 19  |
| EP      | 89662 | 25    |     |     | B1      | 200    | 41103 |        |        |       |     |     |       |            |     |
|         | R:    | AT,   | ΒE, | CH, | DE,     | DK, ES | , FR, | GB, GE | R, IT, | LI,   | LU, | NL, | SE, 1 | 1C, 🖸      | PΤ, |
|         |       | ΙE,   | FΙ  |     |         |        |       |        |        |       |     |     |       |            |     |
| CN      | 12120 | 016   |     |     | Α       | 199    | 90324 | CN     | 1997-  | 19244 | 2   |     | 199   | 702        | 19  |
| NZ      | 3312  | 98    |     |     | Α       | 200    | 00327 | NZ     | 1997-  | 33129 | 8   |     | 199   | 702        | 19  |
| JP      | 2000! | 50530 | 00  |     | ${f T}$ | 200    | 00509 | JP     | 1997-  | 53028 | 9   |     | 199   | 9702       | 19  |
| JP      | 34692 | 247   |     |     | B2      | 200    | 31125 |        |        |       |     |     |       |            |     |
| AT      | 28152 | 28    |     |     | ${f T}$ | 200    | 41115 | AT     | 1997-  | 90667 | 5   |     | 199   | 702        | 19  |
| ES      | 22328 | 860   |     |     | Т3      | 200    | 50601 | ES     | 1997-  | 90667 | '5  |     | 199   | 702        | 19  |
| US      | 6045  | 793   |     |     | Α       | 200    | 00404 | US     | 1998-  | 87581 | .1  |     | 199   | 802        | 19  |
| PRIORIT | Y APP | LN.   | NFO | . : |         |        |       | US     | 1996-  | 11800 | P   | P   | 199   | 9602       | 21  |
|         |       |       |     |     |         |        |       | WO     | 1997-  | US258 | 8   | W   | 199   | 9702       | 19  |
|         |       |       |     |     |         |        | -     |        |        |       |     |     | ~     | <b>,</b> , |     |

The invention relates to RNases derived from a native RNase found in the occytes of Rana pipiens. Various humanized and recombinant forms of these mols. are described as well as uses for them. Thus, chimeric RNases were produced with recombinant Escherichia coli. These RNases were shown to inhibit protein synthesis in rabbit reticulocyte lysates and in 4 human tumor cell lines (ACHN, renal carcinoma cells; MDA-MB-231, breast carcinoma cells; SF-539, glioma cells; and HS 578T, breast cancer cells).

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· (FILE 'HOME' ENTERED AT 12:20:26 ON 09 FEB 2007)

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 12:20:43 ON 09 FEB 2007 SEA (RNAS? OR RIBONUCLEAS?) (S) PIPIEN?

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- 5 FILE AQUASCI
- 2 FILE BIOENG
- 29 FILE BIOSIS
- 5 FILE BIOTECHABS
- 5 FILE BIOTECHDS
- 10 FILE BIOTECHNO
- 2 FILE CABA
- 36 FILE CAPLUS
- 1 FILE CIN
- 4 FILE DDFU
- 90 FILE DGENE
- 2 FILE DISSABS
- 6 FILE DRUGU
- 17 FILE EMBASE
- 16 FILE ESBIOBASE
- 12 FILE GENBANK
- 6 FILE IFIPAT
- 6 FILE IMSDRUGNEWS
- 1 FILE IMSRESEARCH
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- 19 FILE MEDLINE
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5 FILE WPIDS

5 FILE WPINDEX

6 FILE NLDB

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237 SEA (RNAS? OR RIBONUCLEAS?) (S) PIPIEN?

193 SEA L2 (S) (GENE? OR DNA? OR RNA? OR MRNA? OR CDNA? OR POLYNUCLE OTI? OR NUCLEIC?)

126 SEA L3 (S) (ISOLAT? OR CLON? OR CHARACTER? OR PURIF? OR EXPRESS? OR RECOMBINAN?)

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